

A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms

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Objectives: To determine whether plant-derived cannabis medicinal extracts (CME) can alleviate neurogenic symptoms unresponsive to standard treatment, and to quantify adverse effects.

Design: A consecutive series of double-blind, randomized, placebo-controlled single-patient cross-over trials with two-week treatment periods.

Setting: Patients attended as outpatients, but took the CME at home.

Subjects: Twenty-four patients with multiple sclerosis (18), spinal cord injury (4), brachial plexus damage (1), and limb amputation due to neurofibromatosis (1).

Intervention: Whole-plant extracts of delta-9-tetrahydrocannabinol (THC), cannabidiol (CBD), 1:1 CBD:THC, or matched placebo were self-administered by sublingual spray at doses determined by titration against symptom relief or unwanted effects within the range of 2.5–120 mg/24 hours.

Measures used: Patients recorded symptom, well-being and intoxication scores on a daily basis using visual analogue scales. At the end of each two-week period an observer rated severity and frequency of symptoms on numerical rating scales, administered standard measures of disability (Barthel Index), mood and cognition, and recorded adverse events.

Results: Pain relief associated with both THC and CBD was significantly superior to placebo. Impaired bladder control, muscle spasms and spasticity were improved by CME in some patients with these symptoms. Three patients had transient hypotension and intoxication with rapid initial dosing of THC-containing CME.

Conclusions: Cannabis medicinal extracts can improve neurogenic symptoms unresponsive to standard treatments. Unwanted effects are predictable and generally well tolerated. Larger scale studies are warranted to confirm these findings.

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Introduction

Delta-9-tetrahydrocannabinol (THC) and other cannabinoids have been shown¹ to ameliorate both tremor and spasticity in a well-validated animal model of multiple sclerosis (MS). There are many anecdotal reports^{2,3} that cannabis can relieve some of the troublesome symptoms of MS and spinal cord injury. Open or single-blind observations in a small number of patients have given some support to these reports.⁴⁻⁶ Two small placebo-controlled studies^{7,8} indicated that THC in doses between 5 and 10mg orally was significantly superior to placebo in relieving spasticity with minimal adverse effects, and Martyn *et al.*⁹ reported that nabilone relieved muscle spasms and nocturia better than placebo in a study of a single case. Recent scientific reviews in the UK¹⁰ and the USA¹¹ have renewed interest in cannabis-derived medicines, but there are also dissenting voices¹² and studies suggesting caution.¹³ In this context, and given the legal and social arguments that continue, systematic research into the risks and benefits that may be associated with cannabis-derived medicines is required.

Recently, standardized whole-plant cannabis medicinal extracts (CME) have become available for clinical research. This is important because many components of the plant other than THC may have therapeutic potential or synergistic activity.¹⁴ These include nonpsychoactive cannabinoids such as cannabidiol (CBD), as well as various terpenoids and flavonoids. CBD is of particular interest because of its potent antioxidant and anti-inflammatory properties, along with the possibility that it may modulate unwanted THC effects.¹⁴ Selective breeding, a computer-controlled growing environment, and rigorous analytic procedures during extraction can be used to ensure the purity and stability of these extracts.¹⁵ Choice of delivery system remains critical to the successful clinical application of CME. Smoking is inappropriate for a pharmaceutical product, and bioavailability from the gastrointestinal tract is unpredictable. The sublingual route has been selected because it lends itself to self-titration by the patient and provides a satisfactory pharmacokinetic profile.¹⁶

This exploratory trial was designed as a pilot for future large-scale cohort studies. It set out to explore the practicalities of patient self-titration, to identify a satisfactory pattern of dosing, to establish whether neurogenic symptoms could be alleviated by sublingual CME, and to identify potential adverse effects. Its design was limited by various legal considerations relating to the medical use of CME within the UK at the time.

Methods

The sample was drawn from local neurological rehabilitation outpatient clinics, individual patients who had heard of the project locally, and a database of patients who had contacted GW Pharmaceuticals to register their interest in taking part in research. Eligible patients had to have a neurological diagnosis and to be able to identify troublesome symptoms which were stable and unresponsive to standard treatments. The most predominant of these were neuropathic pain, spasticity, muscle spasms, impaired bladder control and tremor. Patients were excluded if they had a history of: drug or alcohol abuse, serious psychiatric illness (excluding depression associated with the neurological condition), serious cardiovascular disease or active epilepsy. The study was approved by the local research ethics committee.

After giving full informed consent to participate, each patient was screened for suitability and up to five target symptoms identified. Those patients taking other supplies of cannabis were asked to stop for four weeks before entry, and not to take any during the study. Assessments were conducted at baseline and then at the end of each two-week study period. The overall study flow of patients is shown in Figure 1.

The following measures were used. Subjects kept a daily diary in which they scored their target symptoms by means of visual analogue scales (VAS) at the same time each day. They also used VAS to provide a daily record of subjective intoxication, alertness, appetite, happiness, relaxation, optimism, energy, general well-being, sleep and feeling refreshed.

At each two-weekly assessment visit, the subjects completed the Short Orientation-Memory-

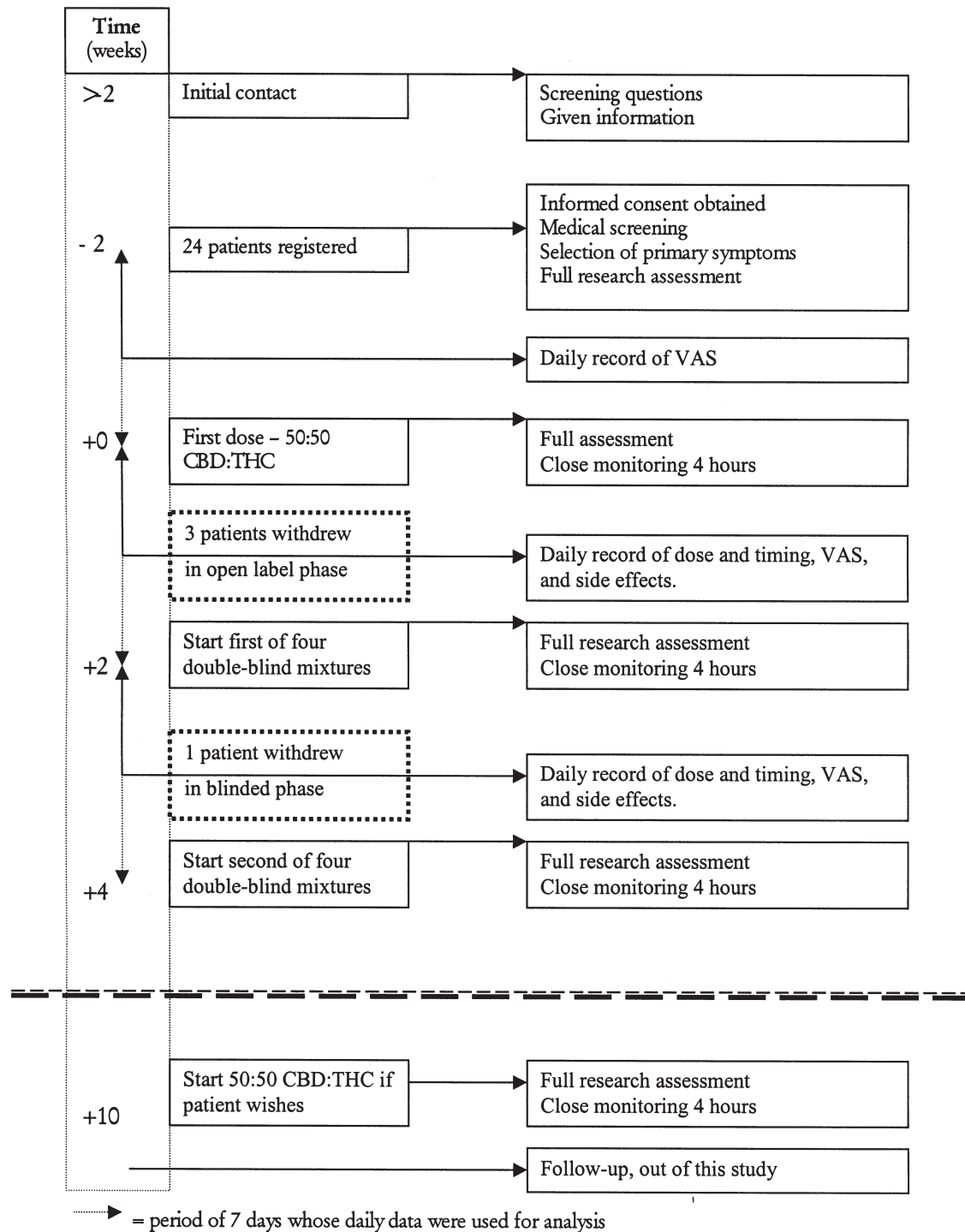


Figure 1 Study protocol

Concentration (SOMC) test,¹⁷ the Barthel Activities of Daily Living Index,¹⁸ the Rivermead Mobility Index,¹⁹ and the General Health Questionnaire 28.²⁰ The following measures were taken when applicable: Ashworth scale for spasticity²¹; Nine Hole Peg Test of manual dexterity²²; 10-metre timed walk; numerical rating scales of fatigue, pain, spasticity, bladder urgency and urinary incontinence, and frequency of muscle spasms and nocturia.

The test articles were whole-plant extracts of delta-9-tetrahydrocannabinol (THC-rich CME), cannabidiol (CBD-rich CME) and a 1:1 preparation of the two (THC:CBD). These were presented in a pump-action sublingual spray that delivered 2.5 mg THC and/or CBD at each actuation. The maximum permitted dose of each CME was 120 mg / 24 hours. The placebo spray contained inert plant material and solvent only. All preparations incorporated a peppermint flavour to disguise the taste of CME. Patients continued to take all previously prescribed medication but were asked not to take any other cannabis during the study.

Following a drug-free run-in period and baseline assessments, the first period of dosing was with open label THC:CBD in order to familiarize the subject with procedures and ensure they could tolerate a CME. First dosing for each treatment period took place in clinic under nursing and medical supervision, and was followed by a two-week period of home dosing. The initial clinic regime permitted up to eight sprays (20 mg of THC and/or CBD) to be administered over a period of 70 minutes. This sometimes resulted in marked intoxication, so from subject 8 onwards the maximum clinic dose was reduced to four sprays over 2 hours. Patient 14 became intoxicated after four sprays, so for subsequent patients initial dosing was further reduced to two sprays over 2 hours. All patients were closely monitored for 4 hours after the start of dosing.

On leaving the clinic patients were instructed to increase their dose cautiously over the first week of each period, monitoring benefit and adverse effects, until an optimal dose was obtained. The timing of each spray was recorded in the daily diary. Research nurses maintained regular telephone contact to check on the patient's well-being and ability to use the spray.

After the first two-week period using open-label known THC:CBD, the patient entered an eight-week double-blind study phase with four two-week stages using THC:CBD, or CBD alone, or THC alone, or placebo. Randomization was achieved using Williams' squares, and vials for each two-week period were allocated and coded before despatch to the investigators. The patient was then given a supply of vials to use over each two-week period. Initially, for ethical reasons, patients were allowed a supply of open-label THC:CBD as 'rescue' medication during the cross-over trial but were encouraged to use it as sparingly as possible. Results from the subgroup of patients who used zero or negligible amounts of rescue medication were subjected to separate statistical analysis.

At the end of the double-blind cross-over study, patients were allowed to continue on active medication as part of a long-term safety and tolerability study if they chose to do so.

Since the first week of each treatment period was spent titrating up to optimal dosing patterns and may have been compromised by carry-over effects, daily VAS scores were averaged for days 8–14 in each period for comparison between periods. Data collected at each assessment point were analysed in their entirety. Treatments during the double-blind periods were compared using analysis of variance with patient, period and treatment as factors. Least square means for each treatment and the difference in least square means between each active treatment and placebo were calculated. In addition, comparisons were made between baseline and placebo using paired *t*-tests. A two-sided significance level of 5% was used to determine statistical significance.

Results

Twenty-four patients were enrolled into the study, and three of these withdrew during the open label THC:CBD period. One could not get benefit without intoxication, one had a vasovagal episode during first clinic dosing, and one developed a sublingual burning sensation. Data from one other patient could not be included because, owing to marked sensitivity to the psychoactive effects of THC, she did not complete all treat-

ment periods. Half the sample reported having used cannabis for medicinal purposes on at least one occasion in the past, but none had done so within the previous six months. Twenty patients (10 males) completed the study, of whom 14 had multiple sclerosis (MS), four had spinal cord injury, one had a brachial plexus lesion and a neuropathy, and one had an amputation with pain in the phantom limb. Average age of the sample was 48 years, and distribution of target symptoms was as follows: pain = 13; muscle spasms = 17; spasticity = 9; impaired bladder control = 11; tremor = 8. Twelve patients used zero or negligible amounts of rescue medication. Data were analysed for the whole sample, and separately for the rescue-free group. This analysis revealed a very similar pattern of responses to outcome measures between the two groups. Plasma samples confirmed that sublingual CME were reliably absorbed.

In Tables 1–3, figures in bold indicate scores in the randomized periods that are statistically different from placebo. Table 1 shows the mean diary VAS scores for the whole sample. In comparison with placebo, CBD CME significantly improved pain, THC CME significantly improved

pain, muscle spasm, spasticity and appetite, and THC:CBD significantly improved muscle spasm and sleep. All three CME produced improvements in other parameters in comparison with placebo that did not reach statistical significance.

Table 2 shows the results from the two-weekly assessments in the whole sample. In comparison with placebo all three CME produced significant improvements in ratings of spasticity, and both THC CME and THC:CBD significantly reduced the frequency of muscle spasms. THC CME reduced SOMC more than the other extracts.

Table 3 shows the doses of test article and rescue medication in each period for the whole sample and rescue-free subgroup, and self-ratings of intoxication. Use of rescue medication did not differ significantly across treatment groups. Level of intoxication was highest following THC CME. In the rescue-free group, average daily intake of sprays was 30% higher in the placebo period than in the active periods.

Individual patients also reported benefits with other symptoms such as co-ordination, bladder and bowel control, and visual acuity but these were not studied systematically.

Table 1 indicates that a placebo effect in rela-

Table 1 Data from daily visual analogue scales. All 20 patients who completed study. Mean (SD) score over last seven days of each two-week period

Phase/drug	Baseline	Known		Unknown		
		CBD:THC	CBD	THC	CBD:THC	Placebo
Symptom (n)						
Pain (12)	30.1 (17.8)	40.3 (25.1)	54.8 (22.6)	54.6 (27.4)	51.3 (27.0)	44.5 (22.7)
Spasm (16)	40.9 (18.5)	52.8 (25.9)	54.6 (19.1)	58.4 (22.3)	55.8 (24.4)	47.3 (22.6)
Spasticity (8)	29.0 (16.1)	41.4 (22.9)	47.8 (18.5)	57.3 (22.2)	43.8 (15.6)	42.3 (18.1)
Bladder (10)	44.2 (22.1)	51.6 (29.8)	60.5 (28.4)	56.4 (30.0)	55.7 (30.3)	54.9 (28.8)
Coordination (8)	36.4 (16.4)	43.8 (26.9)	38.3 (22.9)	42.8 (23.7)	40.3 (27.0)	40.6 (21.1)
Alertness (20)	47.5 (20.1)	52.3 (20.3)	56.9 (22.6)	60.4 (21.4)	58.3 (23.2)	56.5 (19.3)
Appetite (20)	46.8 (23.6)	47.8 (23.7)	43.4 (25.4)	45.6 (26.3)	44.4 (26.0)	39.0 (25.9)
Happiness (20)	52.7 (23.5)	56.0 (20.8)	58.6 (22.2)	60.5 (20.1)	61.0 (21.0)	55.3 (16.6)
Relaxation (20)	52.2 (22.2)	55.1 (21.6)	59.9 (23.6)	60.1 (22.5)	60.1 (22.6)	54.8 (19.7)
Optimism (20)	54.3 (24.5)	56.4 (20.7)	58.7 (21.8)	59.6 (20.1)	58.6 (21.9)	54.0 (16.7)
Energy (20)	40.9 (20.3)	49.0 (18.8)	50.1 (19.3)	52.3 (19.1)	50.9 (18.5)	50.5 (16.9)
Well-being (20)	48.2 (21.3)	53.3 (17.6)	55.2 (19.9)	58.0 (17.2)	56.8 (19.5)	52.9 (15.1)
Sleep (20)	47.3 (19.7)	59.9 (21.7)	57.9 (25.1)	61.7 (25.4)	65.3 (22.6)	59.0 (24.4)
Refreshed (20)	38.5 (17.9)	50.8 (22.0)	51.6 (23.5)	52.7 (25.7)	55.2 (24.7)	51.0 (23.8)

Score range: 0 = worst possible, 100 = best possible.

CBD, Cannabidiol; THC, tetrahydrocannabinol.

Bold indicates values statistically significant difference from placebo at $p < 0.05$.

tion to baseline is seen to an appreciable degree (though still nonsignificant) in only a minority of domains.

Unwanted effects that in the investigators'

opinion were definitely, probably or possibly related to study medication and which occurred in more than one subject are shown in Table 4. It must be noted that some patients in all peri-

Table 2 Data from two-weekly assessments. All 20 patients. Mean (SD) score at each assessment point

Phase/drug	Baseline	Known		Unknown			
		CBD:THC	CBD	THC	CBD:THC	Placebo	
Scale	Score, bad-good						
Ashworth	5-0	1.9 (1.1)	1.7 (1.2)	1.7 (1.2)	1.8 (1.2)	1.7 (1.1)	1.7 (1.0)
GHQ	84-0	21.9 (14.1)	14.9 (7.4)	15.5 (9.7)	16.3 (10.2)	17.6 (11.9)	20.1 (11.5)
Barthel	0-20	11.4 (5.7)	10.7 (6.0)	11.2 (6.4)	10.9 (5.8)	10.7 (5.8)	11.1 (6.0)
RMI	0-15	4.5 (4.4)	4.8 (4.7)	4.8 (4.8)	5.1 (4.7)	4.7 (4.8)	4.9 (4.7)
SOMC	0-28	27.1 (1.9)	26.9 (1.6)	26.9 (2.3)	25.7 (3.4)	26.4 (2.7)	26.9 (2.5)
Numerical symptom scale							
Spasticity severity	10-0	6.2 (2.9)	3.7 (2.3)	3.8 (2.0)	3.8 (2.0)	4.1 (1.8)	5.4 (2.3)
Spasm frequency	Per day	5.5 (2.4)	3.6 (2.3)	4.6 (2.2)	3.4 (1.8)	3.6 (1.6)	4.9 (2.5)
Fatigue	10-0	5.2 (2.1)	4.1 (2.5)	4.6 (2.4)	4.2 (2.2)	5.2 (2.5)	5.0 (2.4)
Pain	10-0	5.6 (3.3)	3.5 (3.0)	3.8 (2.9)	3.5 (2.8)	3.9 (2.9)	4.4 (3.2)
Incontinence frequency	Per day	0.9 (1.3)	0.4 (1.0)	0.8 (1.0)	0.5 (0.9)	0.7 (1.4)	0.7 (1.6)
Incontinence severity	10-0	2.9 (3.3)	1.7 (2.7)	1.4 (1.4)	1.2 (1.8)	1.8 (2.8)	1.4 (2.1)
Bladder urgency severity	10-0	4.1 (3.6)	3.2 (3.6)	3.2 (3.0)	3.0 (2.7)	3.5 (3.4)	3.3 (3.1)
Nocturia frequency	Per night	1.8 (1.5)	1.2 (2.1)	0.6 (1.3)	1.2 (1.3)	1.4 (2.0)	0.5 (0.8)

CBD, Cannabidiol; THC, tetrahydrocannabinol; GHQ, General Health Questionnaire 28; RMI, Rivermead Mobility Index; SOMC, Short Orientation-Memory-Concentration test.

Bold indicates values statistically significant difference from placebo at $p < 0.05$.

Table 3 Dosing: sprays/day of trial and rescue medication. Mean (SD) score over last seven days of each two-week period

Phase/drug	Baseline	Known		Unknown		
		CBD:THC	CBD	THC	CBD:THC	Placebo
Treatment (20)	-	9.4 (6.0)	8.9 (7.2)	9.4 (7.2)	8.8 (4.0)	9.9 (7.9)
Rescue (20)	-	-	4.2 (7.0)	2.2 (5.5)	2.7 (6.8)	3.6 (5.7)
In intoxication	-	$n = 16$ 23.7 (19.7)	$n = 17$ 15.6 (19.1)	$n = 18$ 22.0 (18.7)	$n = 20$ 17.5 (17.7)	$n = 19$ 9.2 (13.1)
No rescue group						
Treatment (12)	-	5.8 (1.8)	9.8 (6.5)	9.4 (4.8)	9.1 (4.1)	12.5 (6.4)
Min, max	-	2, 9	2.7, 24.1	5.3, 18.0	2.9, 16.0	6.0, 30.4
In intoxication (12)	-	24.1 (18.7)	16.2 (21.1)	25.2 (19.2)	19.0 (18.2)	8.9 (11.8)

In intoxication VAS: Score range: 0 = none, 100 = severe.

CBD, Cannabidiol; THC, tetrahydrocannabinol.

Bold indicates values statistically significant difference from placebo at $p < 0.05$.

Table 4 Patients with adverse events possibly, probably or definitely related to trial medication

	THC:CBD open label (n = 24)	CBD-rich CME (n = 21)	THC-rich CME (n = 20)	THC:CBD (n = 20)	Placebo (n = 21)
'Drug toxicity'	9	0	1	1	0
Headache	1	1	3	1	2
Nausea	1	1	1	1	3
Vomiting	1	0	1	1	2
Diarrhoea	0	1	2	1	1
Sore mouth	3	1	1	0	0
Sleepiness	1	0	1	2	1
Fall	0	1	1	1	1
Cough	0	0	1	1	0
Impaired balance	1	0	1	1	0
Fatigue	0	0	0	1	1
Influenza-like symptoms	0	0	0	1	1
Thirst	0	1	0	1	0
Disturbance in attention	1	0	1	0	0
Dizziness	1	0	0	0	1
Hypoaesthesia	1	1	0	0	0
Hypotension	1	0	0	0	1
Anxiety	0	0	0	0	2
Depressed mood	0	1	1	0	0
Number of patients with one or more adverse events:	16 (67%)	7 (33%)	11 (55%)	6 (30%)	10 (48%)

ods took rescue medication (THC:CBD). Four subjects reported soreness or numbness of the mouth or throat.

Discussion

This preliminary study demonstrates that CME can alleviate previously intractable neurologically based symptoms, including pain, spasms and spasticity in some patients. Intoxication seemed to be primarily associated with THC CME but even here was usually of tolerable intensity.

CBD CME appeared to have analgesic and anti-spasticity properties in its own right. These findings, which require independent confirmation, are potentially important because CBD is nonpsychoactive and has a relatively benign adverse event profile.

Early experience with rapid initial dosing with THC:CBD indicated the need for more gradual introduction to CME. When over-dosing did take place supportive measures were all that were required. Patients disliked intoxication and wished to avoid it, in contrast to recreational users. During self-titration this was the dose-lim-

iting effect in several patients, and was the primary reason for withdrawal in three cases. However, with careful self-titration most patients were able to achieve useful symptom relief at a subintoxication dose. Soreness from the alcohol solvent was noted in a few patients and caused one to withdraw.

No patients were suspected of abusing CME, and most used doses that were much less than the

Clinical messages

- Cannabis medicinal extracts (CME) may alleviate neurogenic spasticity, muscles spasms and bladder dysfunction in some patients.
- CME may also help reduce poor sleep and poor appetite.
- Side-effects of sublingual cannabis medicinal extracts included hypotension when administered too quickly, and intoxication occasionally.
- Further research on CME is warranted.

maximum permitted. Some patients had the drug administered by family members or paid carers and again there were no practical problems.

The study had methodological limitations as a consequence of the need to adopt a cautious design, primarily to protect patients but also to satisfy regulatory authorities. It was felt necessary to demonstrate patients' ability to tolerate a cannabis derivative by exposing them to a two-week period on open-label THC:CBD before embarking on the double-blind study. Initially, access to THC:CBD as 'rescue medication' during the randomized crossover was allowed to allay potential loss of benefit when moving from active to inactive medication. After experience with 13 patients it was felt that rescue medication was not required ethically or in practice. This decision was endorsed by the research ethics committee. However, although patients had prior experience of active medication, they did not use much rescue medication suggesting that they were truly unaware of what drug was being given.

The patients were heterogeneous both in terms of underlying diagnosis and in terms of the main troublesome symptoms. A large number of measures were used, many of them visual analogue scales or numerical rating scales. The analysis involved a large number of statistical comparisons. Consequently it is possible that some statistically significant results arose through chance. However, the positive findings are internally consistent and in keeping with existing evidence from basic science and anecdotal patient reports. The emergent side-effect profile was consistent with expectations for cannabis-based medicines.

A third potential area of concern is the great variability in dose used. This obviously might reduce the likelihood of detecting an effect, but conversely it allows the patient to titrate to an effective dose without side-effects. Dose titration is common when using symptomatic treatments such as this.

A final area of concern is that patients may have self-selected as being particularly responsive to cannabis. The main purpose of this study was to determine if there was any evidence of a beneficial response, and so this was not of great concern. However it should be noted that only half had any previous experience of cannabis, and also that most drug interventions probably only

help a proportion of all patients taking the drug.

In conclusion, this preliminary investigation suggests that sublingual CME may be an effective treatment for resistant symptoms associated with neurological diseases including pain, muscle spasms and spasticity, impaired bladder control, reduced appetite and poor sleep. Larger scale studies to confirm these findings and further explore the utility of CME are now required.

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Competing interests

PR also holds the post of Medical Director with GWP. PM and HH are funded for this research by GWP. The NOC NHS Trust was reimbursed by GWP for DW's time spent in the study.

Contributions

All authors contributed to the design and running of the study, and to writing the paper. DW is the guarantor.

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